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Cortical Control of Nociceptive Transmission from the Heart

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Depriming effect of the cerebral cortex (predominantly of zones 1 and 2 of viscerosomatic sensitivity) on transmission of the cardiac afferent signals with a subcortical nociceptive component, which were provoked by electrical stimulation of the sinoatrial node of the heart conduction system, was established in experiments on cats. The agonist of opiate M-receptors morphine considerably potentiated the effect of cortical stimulation, while opiate receptor blocker naloxone antagonized it.

Key Words: *cerebral cortex; descending control; nociception; heart*

Clinical practice and physiological experiments demonstrated the important role of the cerebral cortex (CC) in perception and regulation of pain [2,10]. One of the components of cortical antinociceptive mechanism is descending inhibition of the nociceptive traffic from cutaneous or pulpal afferent somatic nerves in the spinal cord and supraspinal structures [1,2,10].

Our aim was to study cortical effect on transmission of visceral nociceptive signals and to elucidate the role of opiatergic mechanisms in this process. The source of afferent signals was the sinoatrial node (SAN) of the cardiac conducting system.

MATERIALS AND METHODS

Experiments were carried out on cats weighing 2.5-3.7 kg, which were narcotized intraperitoneally with chloralose (30-60 mg/kg), paralyzed with gallamine triethiodide, and artificially ventilated. Electrical stimulation was applied to SAN innervated by spinal afferent system of the heart [3,4,11]. Bipolar silver stimulating electrodes had contact area of 0.1 mm^2, the distance between electrodes was 0.5 mm. SAN was stimulated with single rectangular pulses (0.3 msec, 10-15 mA, and 0.3 Hz repetition rate).

Conditioning stimulation was applied to various regions of the anterodorsolateral CC (right hemisphere) via bipolar electrodes (1 mm contact diameter, the distance between electrodes was 1.5 mm). The duration and amplitude of the stimuli were 0.1 msec and 1.3 mA, respectively. Localization of the electrodes on the cortical surface was determined by detailed corticography [4]. The interval between conditioning and test stimuli was 150 msec.

Potentials evoked by SAN stimulation were recorded in the thalamic nuclei (n.VPL and n.CM), periaqueductal gray matter (SGC), anterior (AHA), and posterior (AHP) hypothalamus. We used monopolar steel electrodes insulated along the entire length except the tip (diameter 50 μ). The electrodes were inserted into the subcortical structures in accordance with stereotactic coordinates [6,9]. Electrode localization was verified histologically on cerebral sections by anode coagulation mark.

To qualitatively estimate the corticifugal influences, we compared (in percents) the initial amplitude of the first two phases (or amplitude of a single phase in monophasic response) in evoked potentials with the same parameters recorded during cortical stimulation. The results were analyzed by averaging technique with a Multibus discrete-summation device (OTE Biomedica).

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To evaluate the autonomic components of the nociceptive reaction during SAN stimulation, the experimental paradigm included invasive measurement of arterial pressure and recording of iris movements (mydriasis). To this end, a linearly diaphragmed light beam was directed to the iris. The reflected beam was transformed by a photodiode into potential and recorded after amplification. The chemicals used in this study were morphine hydrochloride (Belmedpreparaty) and naloxone (Sigma), which were injected intravenously in isotonic NaCl.

RESULTS

Electrical stimulation of SAN evoked positive-negative and monophasic potentials in the studied subcortical structures, which had different amplitude and latency. Conditioning stimulation of CC zones corresponding to different subcortical structures decreased the total amplitude of evoked potentials by 20-50% and more. Electrical stimulation of the cortical zones corresponding to AHA decreased the amplitude of evoked potentials by more than 50%. This zone corresponded to the squares RB-5, RC-7, and RD-6 in the detailed corticography coordinates situated predominantly in the caudal cortical regions (Fig. 1).

When evoked potentials were recorded in AHP, the effective corticifugal zone occupied a more extensive area (RB-2, RB-3, RB-4, RB-5, RC-3, and RD-4) and corresponded to the first and partially to the second zones of viscerosomatic sensitivity, as well as to associative fields in the rostral and dorsal parts of suprasylvian sulcus. Stimulation of virtually all parts of anterodorsolateral cortex decreased the amplitude of evoked potentials in SGC. However, the maximum effect was observed only when stimulation was applied to the region of dorsal sylvian sulcus (RE-5).

Potent corticifugal influences directed to thalamic intralaminar n.CM (30-50% decrease in total amplitude of the responses) arose from a large area (squares RA-5, RB-1, RB-2, RB-3, RC-2, and RD-3).

The inhibitory influence of CC on the afferent signals was minimum in the specific thalamic n.VPI. The decrease in the amplitude by 30% and more was observed when electrical stimulation was applied to squares RB-2, RB-3, RC-2, RD-3 (zones 1 and 2 of viscerosomatic sensitivity).

Electrical stimulation of SAN induced mydriasis, and increased blood pressure in some cats. Conditioning stimulation of CC prevented mydriasis and hypertensive reactions.

Thus, the conditioning electrical stimulation of CC reduces the amplitude of potentials evoked by test SAN stimulation of the subcortical structures, which attests to inhibition of cardiac afferent signals, in particular of the nociceptive signals by CC.

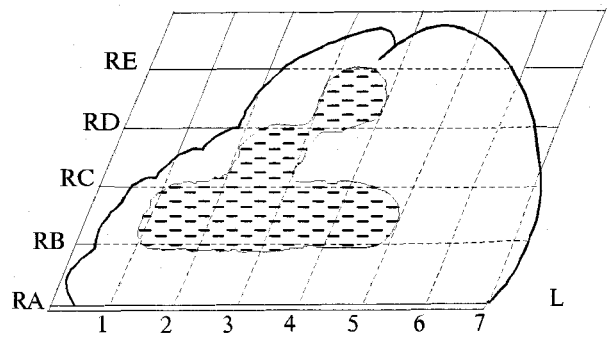

Fig. 1. Corticifugal influences on the dorsal hypothalamic structures. Hatched area of the cortical (corticifugal) zone most pronouncedly affects cardiac afferent traffic.

SAN is one of the most important heart subdivisions [4,11], where in addition to pacemaker cells and sympathetic nerve terminals, the afferent plexuses are concentrated [3].

Afferent signals from the heart reach CNS predominantly via two groups of nerve fibers [4,11]: the first group fibers with vagus nerve branches reach the nucleus of solitary tract in the medulla oblongata; the second group fibers enter the spinal cord via T_1-T_9 dorsal roots. These afferent signals reach directly or indirectly the fifth layer of the dorsal horn in the spinal cord, where they converge with the signals from cutaneous afferent branches. Then the cardiac signals travel via ascending columns to superior structures, including ventrobasal nuclei, medial and intralaminar thalamic nuclei, AHA and AHP, SGC, CC, *etc.* [4]. Some of these structures, such as SGC, thalamus, and CC play an important role in the transition and processing of nociceptive information [2]. Electrical stimulation of SAN produces afferent burst with a nociceptive component. This is confirmed by the fact that the potentials of maximum amplitude were regularly evoked by stimulation that produced the autonomic components of nociceptive reaction: mydriasis and blood pressure rise.

There is evidence on the existence of corticospinal and corticobulbar projections into the nuclei of posterior columns, trigeminal complex, and dorsal horn of the spinal cord [1,2,7]. Moreover, electrophysiological experiments demonstrated both the inhibitory and facilitating effects of CC stimulation on neuronal activity in these structures [14].

Intracortical microstimulation revealed that most pronounced inhibition of spinal neurons induced by noxious and non-noxious stimulation is attained by electrical stimulation of the 3rd, and especially of the 5th and 6th layers [7] containing somas of pyramidal neurons forming the corticospinal pathways. This in-

TABLE 1. Combined Effect of Morphine and Naloxone and Conditioning Stimulation of the Cerebral Cortex on Potentials Evoked by Electrical Stimulation of Sinoatrial Node (*M*±*m*)

Amplitude of evoked potentials, μV	CHS structure	
	n.CM	SGC
Initial	116.6±7.4	115.4±9.7
Morphine, 1 mg/kg	190.4±7.7	193.2±7.25
Cortical stimulation	121.8±8.5	124.6±10.9
+morphine, 1 mg/kg	80.8±7.99	96.6±6.26
+naloxone, 1 mg/kg	203±5.53	215.6±12.96

hibition is accompanied by depolarization of the primary afferent neurons, which is an indication of enhanced presynaptic inhibition. However, apart from direct influence of CC on activity of the segmentary structures involved in nociception, there are other mechanisms modulating nociception. For example, there are anatomical and electrophysiological data indicating connection of CC with midbrain (SGC *et al.*) and medulla oblongata (nuclei raphes *et al.*) structures [1], which play the key role in the natural antinociceptive system [2]. In their turn, these structures control the nociceptive traffic by the descending [2] and rostral [12] influences.

It is noteworthy that among all examined structures AHP is most strongly affected by CC. At the same time, this subdivision receives most part of cardiac nociceptive signals and inhibits the cardiac afferent signals via the hypothalamo-bulbar system [4].

When comparing topography of cerebral areas affecting electrical activity in various subcortical structures, it can be pointed out that zones 1 and 2 of the viscerosomatic sensitivity are the most susceptible. Similar data were obtained in experiments with stimulation of somatic nerves or dental pulp [1,2,5,10].

When studying the role of opiatergic mechanism in the corticifugal control of cardiac nociceptive signals, we showed that morphine (0.5-1.8 mg/kg) considerably increases (by 30-50%) the inhibitory effect of electrical stimulation of CC on the amplitude of potentials evoked in n.CM and SGC (Table 1).

Naloxone (1 mg/kg) produces an opposite effect: it completely blocks the inhibitory corticifugal effect. Moreover, in some experiments naloxone enhanced the amplitude of evoked potentials, which means that naloxone can neutralize the effect of morphine. Similar effects of opiatergic agents on the descending corticifugal control of somatic nociceptive traffic were demonstrated previously [5].

The analgesic effect of morphine and other opiatergic analgetic drugs can be explained by excitation of opiate receptors in the presynaptic membrane of primary unmyelinated afferent fibers. It decreases the release of nociceptive transmitters (substance P *etc.*). It can be assumed that potentiation of cortical inhibition by opioid analgetic drugs is underlain by interaction at the level of primary afferent fibers. In addition, morphine potentiates the descending inhibitory influences of the midbrain and medulla oblongata on nociceptive transmission at the segmental level. When entering SGC and nuclei raphes affected by opioid analgetic drugs, the burst of pulses induced by cortical stimulation can considerably enhance the descending influences of these subdivisions.

Finally, there is evidence on availability of opiate receptors (predominantly of M-subtype) in the 3rd and 4th cortical layers [13]. Cortical application of opiate agonists inhibits activity evoked at the segmental level and in some subcortical subdivisions [8]. Opiate analgetic drugs could significantly enhance efficiency of the cortical structures generating the descending inhibitory trains.

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